DESIGN, SYNTHESIS AND APPLICATION OF AMINO ACID BASED IONIC LIQUIDS IN ORGANIC SYNTHESIS

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Abstract

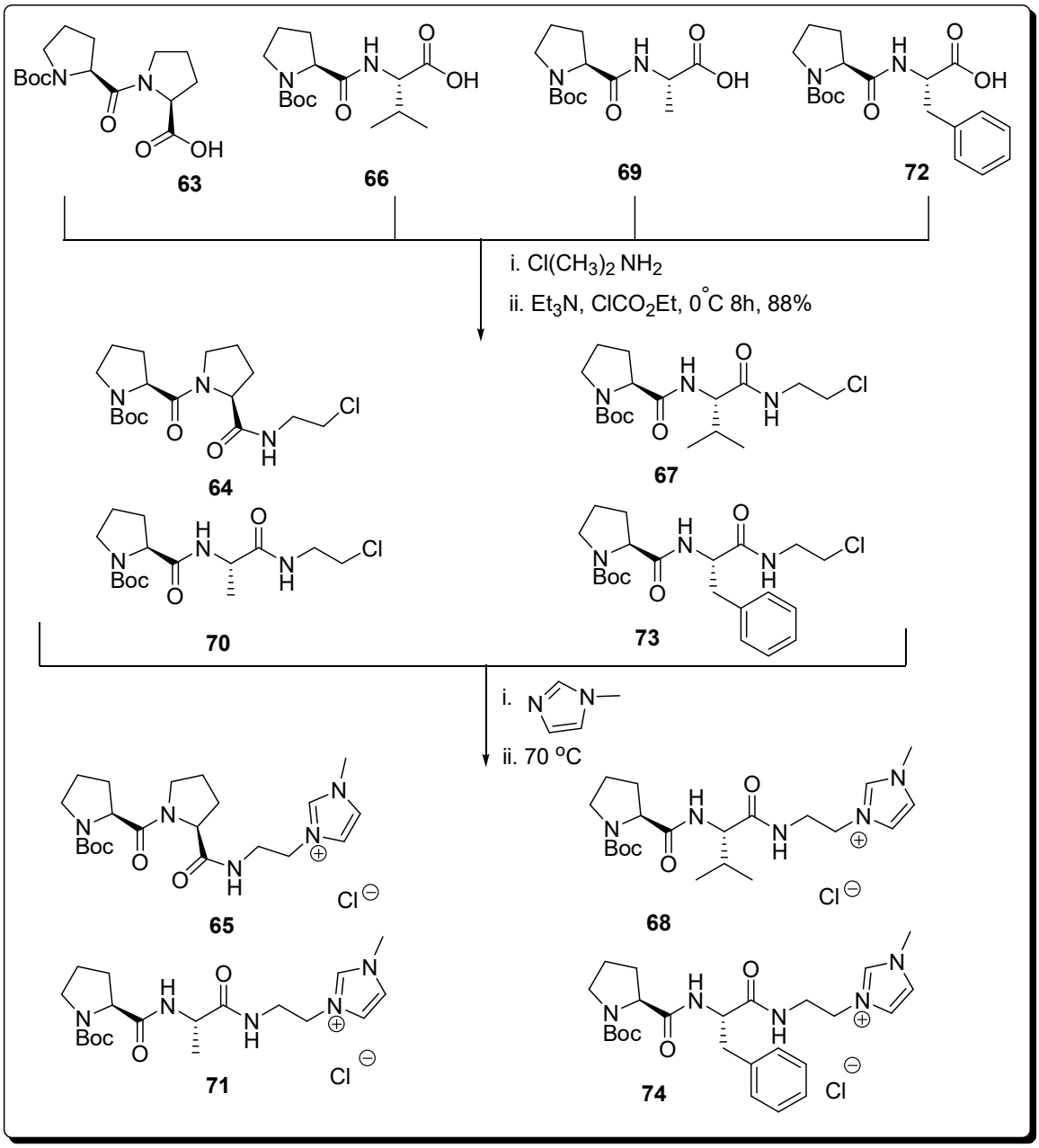
Ionic liquids has appeared as greener catalyst, additives and solvents in organic transformations and showed less pollution, easily disposable and less hazardous than traditional substances. The thesis divided mainly into five chapters. The first chapter describes literature survey of common ionic liquids; amino acid based ionic liquids and recent advances in ionic liquids as catalyst/solvent in organic transformation. Amino acids are used as natural cheap chiral source for the synthesis of amino acid based chiral ionic liquids. Second chapter contains design, synthesis and characterization of novel dipeptide based imidazolium ionic liquids. In third chapter, we described thermal properties of novel synthesized proline functionalized dipeptide imidazolium ionic liquids. The fourth chapter contains new method for the acetylation of alcohols and amines using functionalized ionic liquid as catalyst and acetic anhydride as acylation reagent. The fifth thesis deals with the tritylation reaction of alcohols in presence of Lewis acid based ionic liquid as catalyst and Tr-OH/MTr-OH as tritylating agents.

Chapter 1: Introduction of Ionic Liquids

This chapter deals with a brief literature survey on the common ionic liquids, poly ionic liquids, metallic complex based ionic liquids, amino acid based ionic liquids and task specific functionalized ionic liquid and scope of these ionic liquids as catalyst and solvent in organic transformation.

Chapter 2: Design, Synthesis and Characterization of Dipeptide Based Imidazolium Ionic Liquids

Amino acids are used as natural cheap chiral source for the synthesis of amino acid based ionic liquids. Amino acids can be easily incorporated as both anions and cations in ionic liquids synthesis.



Scheme 1.0: Syntheses of dipeptide-based imidazolium ionic liquids

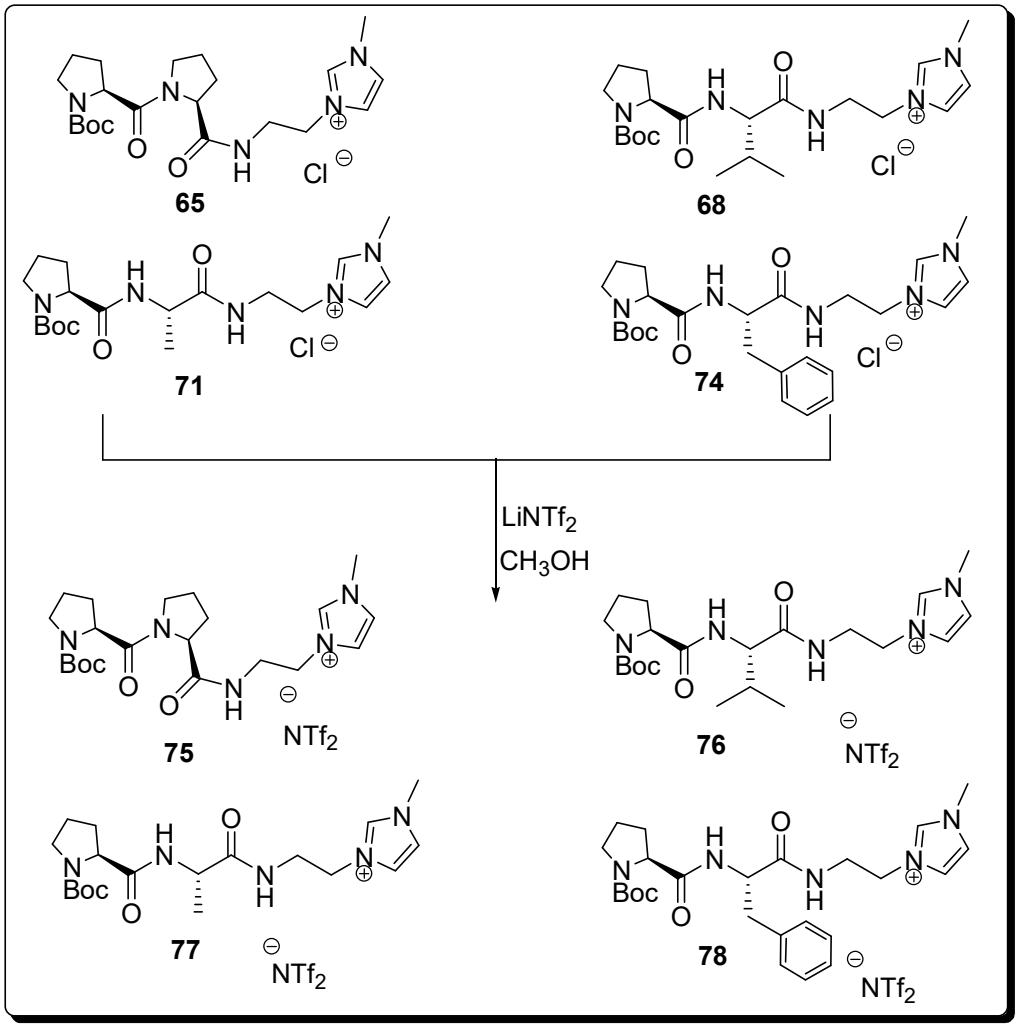
In this chapter, we have described the synthesis and characterization of dipeptide based imidazolium ionic liquids. Syntheses of dipeptide-based imidazolium ionic liquids were carried out as shown in Schemes 1.0.

Boc-Pro-OH was coupled with H-Pro-OMe.HCl/H-Val-OMe HCl/H-AlaOMe.HCl/H-Phe-OMe.HCl using ethyl chloroformate. The resulting dipeptides were hydrolyzed with NaOH to produce dipeptides 63, 66, 69 and 72 with free carboxylic acid (Scheme 1). Dipeptides 63, 66, 69, 72 with free carboxylic acid were covalently coupled with chloroethylamine hydrochloride using ethyl chloroformate and triethylamine to yield 2-chloroethylamide containing dipeptides Boc-Pro-Pro-2-chloroethylamide (64), Boc-Pro-Pro-2-chloroethylamide (67), Boc-Pro-Val-2-chloroethylamide (70), Boc-Pro-Ala-2-chloroethylamide (73), respectively. Reaction of compound 64, 67, 70 and 73 with 1-methylimidazole yields Boc-[Pro-Pro-EMIM][Cl] (65), Boc-[Pro-Val-EMIM]-[Cl] (68), Boc-[Pro-Ala-EMIM][Cl] (71), Boc-[Pro-Phe-EMIM][Cl] (74). Structures of synthesized compound were characterized ^{1}H, ^{13}C NMR, FT-IR and mass spectroscopy.

Chapter 3: Thermal Properties of Proline Functionalized Dipeptide Imidazolium Ionic Liquids

Fluorinated bulky anion such as BF_4, PF_6, and NTf2 etc. plays an important role in thermal stability of ionic liquids. Keeping this in mind we performed exchange of chloride ion from synthesized dipeptide ionic liquids with $LiNTf_2$ (trifuoromethanesulfonimide lithium salt) to yield dipeptide-based imidazolium ionic liquids with NTf_2 anion. In chapter 3 chloride anion of amino acid based ionic liquids Boc-[Pro-Pro-EMIM][Cl](65), Boc-[Pro-Val-EMIM]-[Cl] (68), Boc-[Pro-Ala-EMIM][Cl] (71), Boc-[Pro-Phe-EMIM][Cl] (74) was exchange with

$LiNTf_2$ to yield corresponding amino acid based imidazolium ionic liquids with NTf2 Boc-Pro-Pro-EMIM.(NTf_2) (75), Boc-Pro-Val-EMIM.(NTf_2) (76), Boc-Pro-Ala-EMIM.(NTf_2) (77), Boc-Pro-Phe-EMIM.(NTf_2) (78) (Scheme 2). The Parameters used in evaluating thermal analysis are i) Mass loss percentage ii) Onset Temperature (T_{onset}) iii) Peak Temperature (T_{peak}) iv) Glass transition (T_g) v) Melting point(T_m).



Scheme 1.1: Proline functionalized dipeptidic ionic liquids

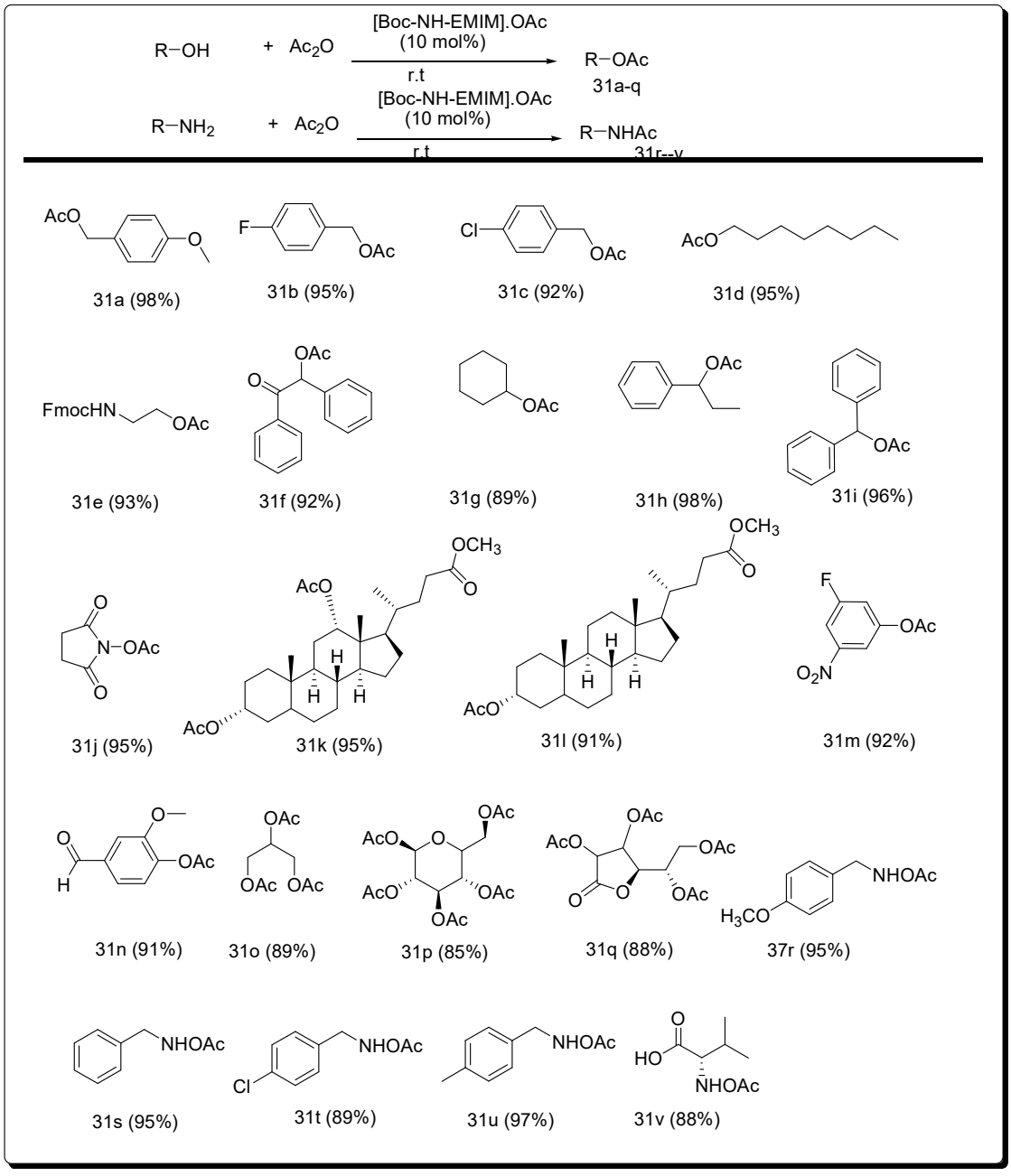
All NTf_2 based DPILs (75-78) are highly viscous and soluble mostly in polar organic solvent whereas chloride based DPILs (65, 68, 71, 74) are soluble in polar solvent but have low viscosity. Water content in all the chloride based DPILs (65, 68, 71, 74) were 0.02, 0.02, 0.04, and 0.02% respectively and it was measure coulometric titration. In future, this AAILs technique can be used for effective formulation of poorly water-soluble drugs in an IL form, and which will eliminates the use of traditional solvent vehicles.

NTf_2 anion containing dipeptide ionic liquid showed high thermal stability as compare to chloride anion because bis (trifluoromethane) sulfonamide (NTf_2) anion due to highly electronegative F atom and stronger hydrogen bonding. Melting point of all the DPILs are below 100^0C and therefore all eight synthesized proline functionalized ionic liquid are room temperature ionic liquid.

Chapter-4: Synthesis of Acetate Anion Supported Ionic Liquid Catalyst for Acetylation Reaction

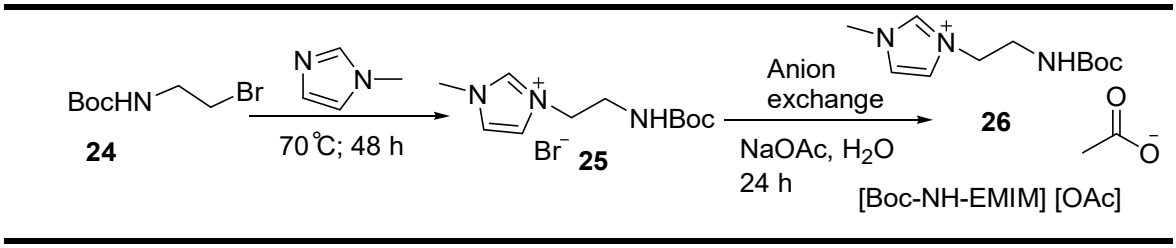
In this chapter, we report the synthesis of task-specific amino-functionalized imidazolium ionic liquid, acetate1-(2-tert-butoxycarbonylamino-ethyl)-3-methyl-3H-imidazol-1-ium; Boc-NH-EMIM.OAc), as an efficient catalyst for the acetylation of alcohols and amines in the presence of acetic anhydride (acetylating reagent). The developed ionic liquid (Boc-NH-EMIM.OAc) was recyclable and reused successfully up to four consecutive cycles without any substantial decay of its catalytic activity. We have been able to show that this acetylating method has many advantages. It gives high yields, takes shorter time, and develops the possibility of benign environmental-friendly process.

Table 1.0: Acetylation reaction alcohol, phenol and amine in the presence of amino functionalized ionic liquid [Boc-NH-EMIM].OAc



A number of experiments were performed to standardize the reaction conditions for acetylation, viz. the effects of solvents, kinds of ionic liquid, mol% of ionic liquid, and types of substrate. An electron-donating group at the aromatic nucleus enhanced the reaction and

gave high yields of the corresponding acetylated products (Table 5, entries 1, 8–10) however, electron-withdrawing groups at the aromatic nucleus delayed the reactions and the yields relatively lower acetylated products compare to electron-donating (Table 5, entries 4, 7). The structures of synthesized acetylated products were confirmed by ^{1}HNMR and ^{13}CNMR spectroscopy.



Scheme 1.2: Synthesis of [Boc-NH-EMIM][OAc] ionic liquid.

We also focus on reusability of ionic liquid, ([Boc-NH-EMIM][OAc]) was reusable four times at shorter time then in fifth cycle, reaction consume more time and catalyst give less yield in acetylation. Structure of [Boc-NH-EMIM] [OAc] catalyst confirmed by ^{1}H NMR, ^{13}C NMR, Mass and IR spectroscopy. We proposed mechanism in presence of acetic anhydride as acetylated reagent, ionic liquid as catalyst and benzyl alcohol as model substrate for acetylation reaction.

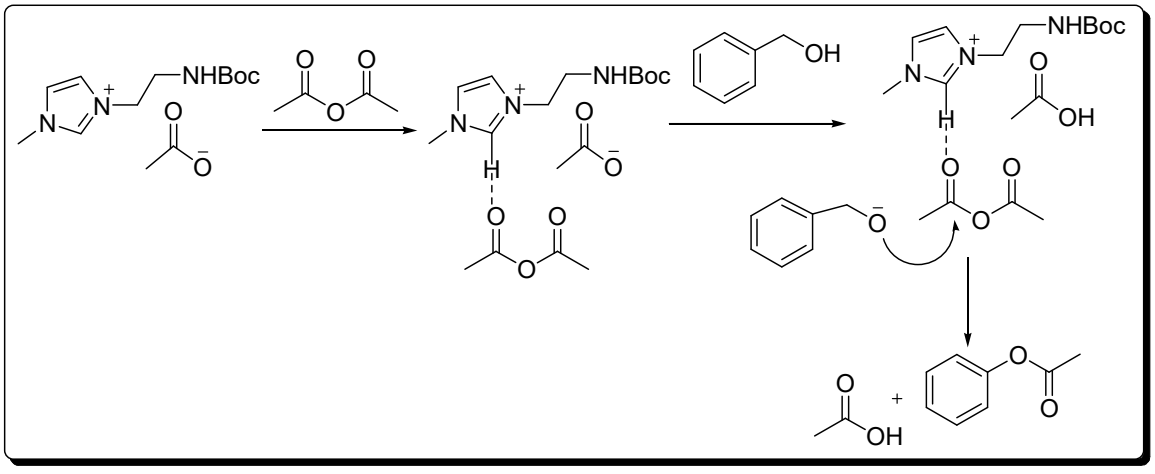


Figure 1.0: Plausible mechanism of acetylation reaction in presence of ionic liquid catalyst

Chapter-5: Lewis Acid Based Ionic Liquid as Catalyst for Tritylation of Alcohols

In this chapter, we have describe tritylation of alcohols with triphenyl methyl alcohol (Tr-OH) and 4-monomethoxyl trityl alcohol (MMTr-OH) in the presence of Lewis acid based recyclable ionic liquids (EMIM·$AlCl_4$) under mild condition. The current method provide good yield of tritylated product in shorter reaction time and the catalyst used in the reaction is recyclable up to three times without any significant loss in yield. Developed catalyst gave selectivity for primary alcohol over secondary alcohol. The present methods recommend that that tritylation of hydroxyl can be performed group without affecting sensitive functionalities (TBDPS, *N*-acetyl, or *N*-Fmoc) present in molecules. 5 Mol% of catalyst (EMIM·$AlCl_4$) along with DCM as solvent is recognized as optimum condition for any tritylation reaction. In accordance with the results of experiments, a reasonable mechanism is drawn and illustrated in figure 5.1.

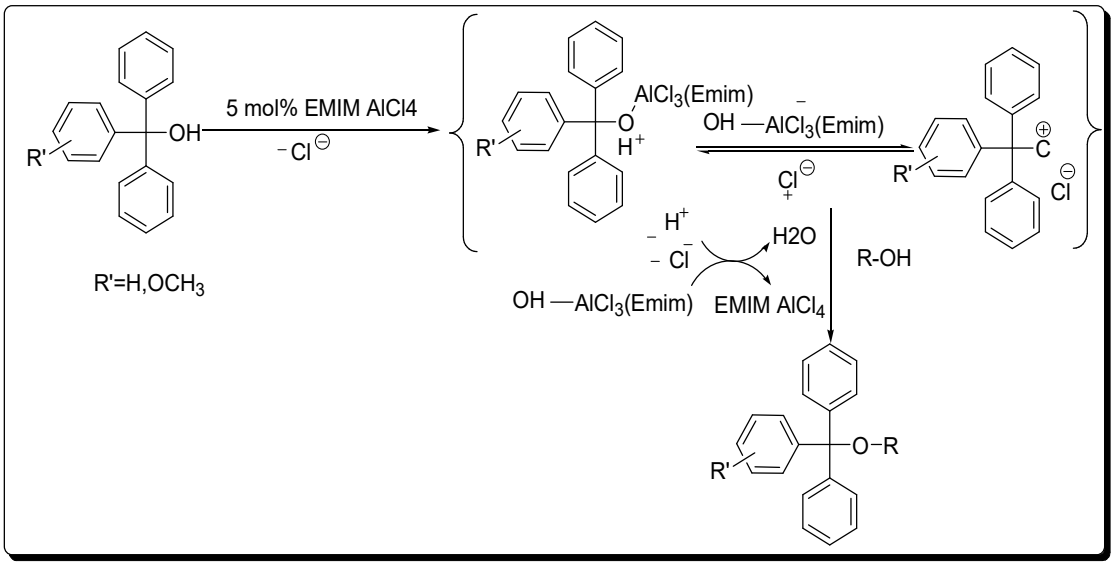
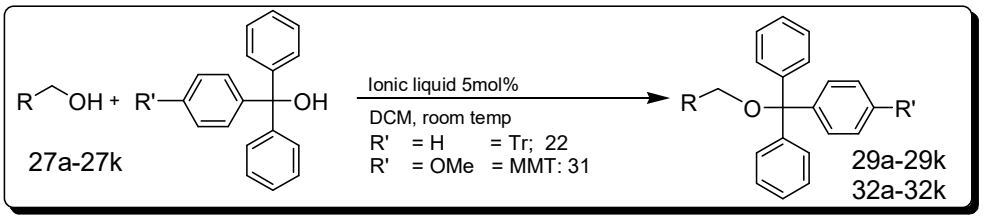


Figure 1.1: Plausible mechanism of tritylation reaction in presence of ionic liquid EMIM·$AlCl_4$

Table 2.0: Tritylation of primary Alcohol in the presence of Lewis acid based ionic acid ($EMIM{\cdot}AlCl_4$)

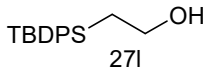
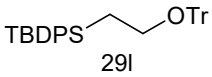
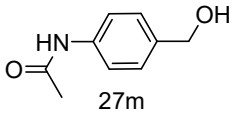
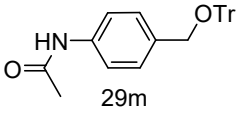
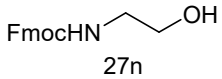
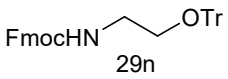
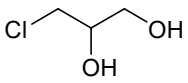
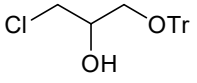
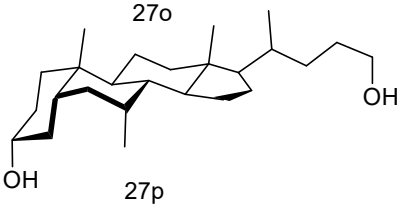
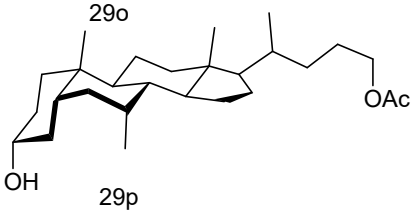


Alcohols (1)	Product (2)	Time (min)	Yield[a]	Product (3)	Time (min)	Yield[a]
HO **27a**	TrO **29a**	30	98	MMTrO **32a**	30	98
HO **27b**	TrO **29b**	25	89	MMTrO **32b**	25	87
HO **27c**	TrO **29c**	60	99	MMTrO **32c**	70	96
HO **27d**	TrO **29d**	30	95	MMTrO **32d**	30	87
HO **27e**	TrO **29e**	30	89	MMTrO **32e**	30	86
HO **27f**	TrO **29f**	45	87	MMTrO **32f**	80	89
HO OCH_3 **27g**	TrO OCH_3 **29g**	70	88	MMTrO OCH_3 **32g**	70	89
HO O **27h**	TrO O **29h**	45	98	MMTrO O **32h**	45	96
HO OCH_3 **27i**	TrO OCH_3 **29i**	50	89	MMTrO OCH_3 **32i**	50	88
HO F **27j**	TrO F **29j**	60	98	MMTrO F **32j**	60	99
HO Cl **27k**	TrO Cl **29k**	50	96	MMTrO Cl **32k**	40	95

Reaction Condition: a) Yield was determined by gas chromatography b) All reactions were carried out using alcohol substrate (1 mmol), Tr/MMTr-OH reagent (1.1 mmol), and (5 mol %) catalyst ($EMIM{\cdot}AlCl_4$) at room temperature

Electron withdrawing group having alcohol furnished excellent yields of the corresponding derivatives (Table 2.0; 29j, 29k and 32j, 32k) compared to that of electron donating group containing alcohol (Table 2.0; 29g and 29i and 32o and 32i). The chemoselectivity is observed for the tritylation of benzyl alcohol in the presence of a phenolic group.

Table 3.0: Tritylation of primary alcohol over secondary alcohol and in the presence of acid/base labile protecting group

Alcohols	Product	Time (min)	Yield
 27l	 29l	50	91%
 27m	 29m	80	90%
 27n	 29n	80	86%
 27o	 29o	50	82%
 27p	 29p	80	80%

Reaction Condition: a) Yield was determined by gas chromatography; b) All reactions were carried out using alcohol substrate (1 mmol), Tr-OH reagent (1.1 mmol), and (5 mol %) catalyst (EMIM·$AlCl_4$) at room temperature

Publications

- **Snehkrishn A. Chaubey**, Jyoti S. Mishra, and Roli Mishra, "*Efficient Approach for the Tritylation of Alcohols Using Recyclable Lewis Acid-Based Ionic Liquid (EMIM•AlCl4)*" ACS Omega **2018**, 3, 9607−9612.
- Roli Mishra, Jyoti. S. Mishra; **Snehkrishn A. Chaubey**, *Recent Advances on Triazolium Ionic Liquids: Synthesis and Application*s. Current Organic Chemistry **2019,** *23* (11), 1239-1255.
- **Snehkrishn A. Chaubey** and Roli Mishra, *Synthesis of task-specific imidazolium ionic liquid as an efficient catalyst in acetylation of alcohols, phenols, and amines.* Chemical Papers, **2020** , 74 ,3259–3268
- **Snehkrishn A. Chaubey**, Niranjan Patra and Roli Mishra**,** *Synthesis of Novel Proline Based Imidazoilum Ionic Liquids,* Monatshefte fur chemie-chemical monthly **2020**, 151, 1409-1417.

Book Chapter

- Roli Mishra, Satyendra Mishra, **Snehkrishn A Chaubey**, Yash B Barot. Book Chapter 10 "Ionic liquids as alternative greener solvents and catalysts in organic transformations" in Book title: Handbook of Greener Synthesis of Nanomaterials and Compounds: Volume 1: Fundamental Principles and Methods. Elsevier Science Editors: Boris Kharisov, Oxana Kharissova **2021**. Pages 359-404 ISBN: 978-0-12-821938-6